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A comparison of two invasive techniques in the management of intractable pain due to inoperable pancreatic cancer: neurolytic celiac plexus block and videothoracoscopic splanchnicectomy

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 VSPL;
 NCPB

Abstract *Background and aims:* Pancreatic cancer is characterized by a constant deterioration in quality of life, excruciating pain and progressive cachexia. The aim of this study was to compare the effectiveness of two invasive methods of pain treatment in these patients: neurolytic coeliac plexus block (NCPB) and videothoracoscopic splanchnicectomy (VSPL) to a conservatively treated control group concerning pain, quality of life and opiates' consumption.

Patients and methods: Fifty nine patients suffering from pain due to inoperable pancreatic cancer were treated invasively with NCPB ($N=35$) or VSPL ($N=24$) in two non-randomised, prospective, case-controlled protocols. Intensity of pain (VAS-pain), quality of life (FACIT and QLQ C30) and opioid intake were compared between the groups and to a control group of patients treated conservatively before the procedure and after 2 and 8 weeks of follow-up. The analysis was performed retrospectively using meta-analysis statistics.

Results: Both methods of invasive pain treatment resulted in significant reduction of pain (VSPL effect size=11.27, NCPB effect size=7.29) and fatigue (effect sizes, respectively, 1.23 and 3.37). NCPB improved also significantly physical, emotional

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and social well-being (effect sizes, respectively, 2.37, 4.13 and 7.51) which was not observed after VSPL. No influence on ailments characteristic for the disease was demonstrated. Mean daily opioid consumption was significantly decreased after both procedures. There was no perioperative mortality and no major morbidity.

Conclusion: Both NCPB and VSPL provide significant reduction of pain and improvement of quality of life in inoperable pancreatic cancer patients. They present rather similar efficacy, but lower invasiveness of NCPB, in combination with its more positive effect on quality of life, pre-disposes it as being the preferred method.

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Introduction

The use of the stepwise World Health Organization analgesic ladder is suggested as the analgesic treatment in patients suffering from inoperable pancreatic cancer (IPC).¹⁻³ Often, the intensity of pain is so high, that opiates are used extensively. Although this approach should be applied in every case when no alternative is available, it should be mentioned that opiates present significant number of physical and psychological complications, including drowsiness, constipation, vomiting, deteriorated communication with family and depression.^{4,5} In rare cases of longer survival, iatrogenic addiction can be observed, adding to the cachectic picture of the disease.⁵ Thus, more invasive methods of pain control need to be considered in IPC patients, including neurolytic coeliac plexus block (NCPL) and videothoroscopic splanchnicectomy (VSPL). Both methods have been well evaluated and reportedly provide satisfactory long-term pain-relief and decrease of the doses of opiates used.⁶⁻⁸ The clinical relevance of pain reduction should be also associated with the fact that pain decrease the survival in pancreatic cancer patients.⁹ This is in line with animal research demonstrating that pain and stress appear to promote tumour growth and result in increased mortality rates.^{10,11}

The aim of the present study was to compare the effectiveness of two invasive methods of pain treatment in IPC patients—NCPB and VSPL—to a conservatively treated control group. Unique of the present study is that the comparison was not limited to mere pain and the use of pain medication, but also broader aspects of quality of life were included in the evaluation.

Methods

Patients

Two groups of patients suffering from pain due to

IPC were treated in two separate, case-controlled, non-randomised studies including treatment with VSPL or NCPB between January 2001 and September 2003 in Department of Surgery, Medical University of Gdansk, Poland. The groups consisted of 14 men and 10 women (VSPL group, $N=24$, M:F ratio=1.4) with mean age of 63.5 years (range 47-78) and 21 men and 14 women (NCPB group, $N=35$, M:F ratio=1.5) with mean age of 61.2 years (range 51-82). The mean time since the diagnosis of the inoperability of the disease was, respectively, 2.1 and 1.7 months, the time from the first symptoms of the chronic pain syndrome was 3.2 and 2.5 months, respectively. In 55 patients (32 in NCPB and 23 in VSPL) the diagnosis was based on open biopsy, and in 37 patients the palliative choledocho-jejunal and gastro-jejunal anastomoses were fashioned before qualifying to further analgesic treatment.

The choice of treatment was based on the decision of the patients and NCPB was usually chosen by patients suffering from pain for a shorter period of time. This approach did not allow to create randomized study but was in agreement with consumeric (orientated towards patients' needs) approach to treatment and was considered more ethical than randomization.

A control group of 39 patients with inoperable pancreatic cancer who were treated conservatively with standard analgesic therapy for chronic pain were used for comparison. The mean age of the group was 67.2 years (range: 52-82). The percentage of women reached 41% similarly to other groups. The onset of the disease was noted at median time of 3.1 months before the initial measurement.

The survival did not affect measures after 2 weeks, but 8 weeks measures could have been taken in 21 (87.5%) patients from VSPL group, 31 (88.6%) from NCPB and 33 (84.6%) from the control group.

Measures

All groups were followed up and measures of pain

and quality of life were taken 2 and 8 weeks after the intervention or in the case of the control group at the corresponding period of time. The pain measure included visual analogue scale-pain and mean daily consumption of opiates quantified in milligrams for all groups. Quality of life assessment included functional assessment of cancer therapy scale (pancreas version) in VSPL group and EORTC QLQ-C30 score for NCPB group. The control group was assessed with both FACIT and QLQ-C30.

Visual analog scale of pain (VAS-pain) is a psychometric tool giving the patient opportunity to express his/her subjective perception of pains, she/he is feeling by drawing a line on a standardized box printed on a sheet of paper. The distance from the zero point to the end of the line drawn by the patient is measured and calculated as a percentage of the length of the box taken as a maximum.

Health-related quality of life is a psychological parameter considered as a multi-factorial measure including different aspects of well-being that may be influenced by the illness. It usually incorporates physical and emotional well-being, functional disturbances, ailments typical for the disease and indirect measure such as social support or fatigue. FACIT and QLQ C-30 tools are well validated for pancreatic cancer patients.^{12,13}

Due to retrospective character of comparison and separate character of protocols, the analytic statistical techniques typically applied in meta-analysis were employed in this study. Raw data was compared using Student's *t*-tests and ANOVA. For meta-analytic like assessment fixed-effects method was used, and effect sizes were calculated as the difference between the outcome means of the groups divided by the pooled standard deviations. An overall weighted effect size was obtained and presented with 95% confidence interval (95% CI). Results were tested for homogeneity using the Breslow-Day tests.

Procedures

NCPB was performed similarly to the method initially reported by Kappis¹⁴ in 1919. Patients were placed in the prone Jack-knife position. After the superficial anaesthesia with 1% lignocaine, the 20G needle (length 10-12 cm) was introduced into the point located 5-7 cm laterally from the midline, just under the lower margin of the 12th rib, towards the trunk of L₁, Th₁₂ vertebrae. The canal of the needle was then anaesthetized with further 6-10 ml of 1% lignocaine. The surface of the vertebra was usually identified at a depth of 6-8 cm. Then, the needle

was rotated 90° towards the vertebra. When the needle bypassed the vertebra by 1-2 cm, and after ensuring it had not punctured the aorta or other major vessel, 20-30 ml of 50% ethanol with 5 ml of 1% lignocaine was injected. The same procedure was repeated for the contralateral side of the vertebral column.

Unilateral VSPL was performed under general anesthesia with single-bronchus intubation. The patient was placed in the right lateral decubitus position with the left arm elevated to 90° angle. They were additionally fixed with support-arms and bandages, and the table was then tilted 30° anteriorly in the longitudinal axis (thus, after induction of a pneumothorax the lung would 'fall away' from the costovertebral gutter). After desufflation of the lung, two trocars were inserted into the thorax: (1) a 5-mm trocar, was placed in the fifth intercostal space in a medial axillary line for the camera, and (2) a 5-mm trocar was placed in the seventh intercostal space in an anterior axillary line for the instruments. After identification of the splanchnic nerve, the parietal pleura was incised and the nerve, together with its minor connecting branches, was prepared to a distance of 5-8 cm and excised. After insufflation of the lung, the trocars were removed, a single chest tube was placed, and the wounds were closed according to standard surgical technique.¹⁵

Results

Both NCPB and VSPL were beneficial for the patients with inoperable pancreatic cancer and resulted in a better quality of life and less pain compared to those patients treated conservatively, both after 2 and 8 weeks of follow-up. The results were estimated basing on average effect size after 2 and 8 weeks of follow-up (Fig. 1).

The positive effect on pain was significantly higher in the VSPL group, and the alleviation of VAS scores was almost twice as strong after VSPL than after the neurolysis. The impact of both procedures on fatigue was significant in both groups, though it was stronger in patients treated with the neurolysis. Interestingly, improvement in social support and emotional well-being was achieved only after neurolysis, while VSPL had no impact on these variables. The physical well-being improved significantly only after NCPB, while there was no influence of VSPL on this parameter. None of the procedures had a positive effect on the ailments typical for the illness.

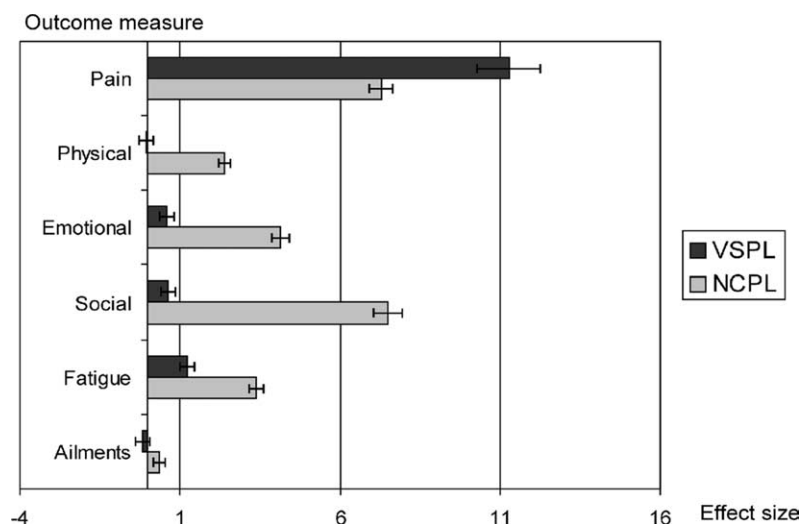


Figure 1 Effect sizes of videothoroscopic splanchnicectomy (VSPL) and neurolytic celiac plexus block (NCPB) in pain treatment of inoperable pancreatic cancer pancreatitis patients compared to control group of patients treated conservatively. Bars show mean effect sizes from two measures: after 2 and 8 weeks of follow-up with 95% CI indicated.

Table 1 represents the findings of the opiates' consumption analysis.

There was no post-operative mortality and no loss to follow-up at 2 weeks due to death. Thirteen patients died before the 8-weeks assessment due to their primary disease: four in NCPB group, three in VSPL group and six in the control group ($p=0.744$). The only morbidity was observed in one VSPL patient, who suffered from intermittent intercostal nerve pain that resolved spontaneously after 2 weeks.

Discussion

The current study compared retrospectively, in meta-analytic fashion two most commonly utilized techniques of invasive pain control in inoperative pancreatic cancer, NCPB and VSPL. Although both techniques have previously been shown to provide significant benefit for the patients, no direct comparison of them has ever been previously attempted. The current results once more

demonstrate that both methods result in a significant short-term pain relief and improvement in quality of life. Without precedence, however, is the finding that, whereas NCPB affects most of the parameters of quality of life, VSPL improves only pain and fatigue. This limited positive effect of VSPL may seem more convincing in light of previous reports concerning chronic pancreatitis patients,^{15, 16} but, on the other hand, the influence of cancer pain on every aspect of quality of life cannot be denied. Achieving a reduction in patients' pain scores may improve their mood and further activity and longevity. Similarly, in a study by Staats et al. the neurolytic block, as compared with medical management alone, not only improved pain, elevated mood, reduced pain interference with activity, but also, what is most encouraging, was associated with an increase in life expectancy.¹⁷ In a randomized study by Wong et al. comparing NCPB and conservatively treated patients, only the subjective perception of severity of pain was improved which may have been subject to the influence of patients' expectations. Moreover, at 1 year, 16% of NCPB patients and 6% of opioid-only

Table 1 Opioid consumption in milligram (mean daily dose \pm standard deviation) before the procedure and in 2 and 8 weeks of follow-up

Group	Before the procedure	2 Weeks ^a	8 Weeks
NCPB ^b	94.3 \pm 9.3	49.3 \pm 9.1 ^c	45.6 \pm 7.6 ^c
VSPL ^b	90.1 \pm 7.7	34.3 \pm 4.6 ^c	41.5 \pm 5.2 ^c
Control ^b	97.2 \pm 8.2	105 \pm 11.4	128 \pm 12.1

^a *t*-Student significant comparison between two invasive treatment groups.

^b Statistically significant differences in ANOVA test comparing different follow-up points in the same group.

^c *t*-Student significant difference comparing invasively treated group to the control group.

patients were alive, though this difference did not reach statistical significance.¹⁸ Lillemoe et al. reported that IPC patients treated with intraoperative chemical splanchnicectomy during explorative laparotomy experienced significantly lower pain and had a lower opioid consumption compared to control patients treated conservatively. In a group of 34 patients with pain before laparotomy, survival was improved in those receiving chemical splanchnicectomy.⁸

The finding that NCPB has a positive effect on emotional well-being is the more important since, there is recent evidence showing that depression may have a negative effect on immune functions and antitumour therapy. This raises the intriguing question whether this treatment is superior in terms of survival in the long run as well.

New methods of imaging provide better and safer approach to NCPB, though interpretation of US or CT images may sometimes provide difficulties.^{19,20} The blind method of needle introduction presented in our material did not produce any morbidity and was successful in all 35 cases. Similarly, Firdousi et al.²¹ presented 30 consecutive patients with blind NCPB without mortality and significant morbidity apart from transient hypotension. They concluded that despite the proximity of vital structures, blind unilateral retrocaval neurolytic coeliac plexus blockade is a safe and effective means to relieve terminal pain associated with upper abdominal visceral cancer.²¹ Recently a laparoscopic method of NCPB in an animal model has been reported.²² It does, however, involve a complex procedure combining laparoscopic ultrasound and endoscopy, thus requiring further research before being considered a possible supplement to pancreatic cancer laparoscopic staging.²²

Videoscopic splanchnicectomy is also reported to be safe and effective procedure in pain treatment both in chronic pancreatitis and pancreatic cancer patients.^{15,23-27} It is associated with low morbidity²³⁻²⁷ and similarly to the current study, with good results in terms of pain relief and improvement of quality of life.²³⁻²⁷ In this study a unilateral splanchnicectomy was chosen due to experience of the surgeons performing the procedures.

The reduction of opioid consumption achieved in the current study due to invasive treatment of pain should not be underestimated. The influence of opioid on escalation of adverse gastrointestinal symptoms has been recently reported.⁵ Mercadante et al. presented a prospective multicenter study, in which 22 patients who underwent NCPB were followed until death. NCPB was effective in reducing opioid consumption and gastrointestinal adverse effects for at least 4 weeks. In the last 4

weeks prior to death, there was the typical trend of increasing symptom intensity common to the terminal cancer population.⁶ These results have also been replicated elsewhere.^{7,28}

Due to the short follow-up, the problem of recurrent pain was not documented in the current study. It does, however, have significant importance to the clinical management of inoperable pancreatic cancer patients. Vranken et al.²⁹ performed a post-mortem on two patients previously treated with NCBP. The neurohistopathologic examination of the celiac plexus revealed an abnormal celiac architecture with a combination of abnormal neurons with vacuolization and normal looking neuronal structures (ganglionic structures and nerve fibers) embedded in fibrotic hyalinized tissue suggesting the neurolytic celiac plexus block with alcohol was capable of partial and only partial destruction of the celiac plexus.²⁹

A solution to this problem may be provided by insertion of celiac catheter. Vranken et al. reported another study on 12 patients who underwent NCPB with alcohol, administered via an indwelling celiac catheter. Two patients remained without pain after the first neurolytic celiac plexus block. In all other patients a second block was administered which provided only temporary relief. Additional intermittent administration of bupivacaine through the catheter was necessary to provide adequate pain relief in these patients. Quality of life increased significantly after the treatment. Opioid consumption decreased in all patients. The authors concluded that NCPB results in a significant but short-lasting analgesic effect, but the use of a celiac catheter can improve the long-term management.³⁰

On the other hand, implantation of foreign bodies such as catheters, carries a risk of infective complications. One alternative would be to use a combination of NCPB and unilateral or even bilateral VSPL. Although, the optimal timing of these interventions remains to be determined, considering that 80-88% of inoperable pancreatic cancer patients present with or eventually develop intractable pain²⁹ and invasive methods of pain relief are associated with minimal morbidity, a case could be made for elective NCPB and/or VSPL.

The limitations of the current study include the relatively small numbers of patients, the retrospective nature, lack of randomization associated with the non-standardized analysis of the quality of life and short follow-up period. Despite this, the results indicate a significant short-term benefit for those undergoing invasive intervention for pain in inoperable pancreatic cancer. Further studies including longer follow-up and survival analysis

with standardized quality of life would be particularly useful.

In conclusion, the present findings suggest that both NCPB and VSPL provide significant reduction of pain and improvement of quality of life in inoperable pancreatic cancer patients. They present rather similar efficacy, but the lower invasiveness of NCPB predisposes it to earlier administration. Given the fact that this method also appears to have a positive effects on broader aspects of quality of life, this is sufficient reason to recommend NCPB as more preferred method.

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